

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
15 November 2001 (15.11.2001)

PCT

(10) International Publication Number  
**WO 01/85718 A1**

(51) International Patent Classification<sup>7</sup>: C07D 403/06,  
403/14, 401/14, 409/06, A61K 31/4166, A61P 25/00

(CH). TROXLER, Thomas, J. [CH/CH]; Sennweg 27,  
CH-4146 Wahlen (CH).

(21) International Application Number: PCT/EP01/05162

(74) Agent: BECKER, Konrad; Novartis AG, Corporate  
Intellectual Property, Patent & Trademark Department,  
CH-4002 Basel (CH).

(22) International Filing Date: 7 May 2001 (07.05.2001)

(25) Filing Language: English

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU,  
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,  
CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,  
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,  
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,  
MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK,  
SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA,  
ZW.

(26) Publication Language: English

(30) Priority Data:  
0011071.8 8 May 2000 (08.05.2000) GB

(71) Applicant (*for all designated States except AT, US*): NO-  
VARTIS AG [CH/CH]; Lichtstrasse 35, CH-4002 Basle  
(CH).

(84) Designated States (*regional*): ARIPO patent (GH, GM,  
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian  
patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European  
patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE,  
IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF,  
CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

(71) Applicant (*for AT only*): NOVARTIS-ERFINDUNGEN  
[AT/AT]; Verwaltungsgesellschaft m.b.H., Brunner Strasse  
59, A-1230 Vienna (AT).

(72) Inventors; and

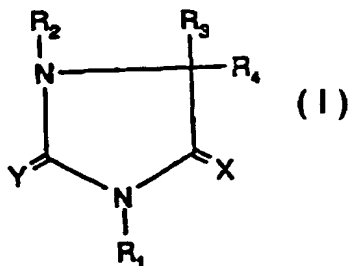
(75) Inventors/Applicants (*for US only*): BERNEY, Daniel  
[CH/CH]; Avenue de France 98, L'Abbey Vd, CH-1004  
Lausanne (CH). BRECKENRIDGE, Robin [GB/CH];  
Rue Wentzwiller 2, CH-68220 Hagental-le-bas (CH).  
NEUMANN, Peter [DE/CH]; Kornhausstrasse 4,  
CH-3013 Berne (CH). SHAPIRO, Gideon [US/US]; 5507  
NW 80th Avenue, Gainesville, FL 32653 (US). SEILER,  
Max, Peter [CH/CH]; Bockrainweg 16, CH-4125 Riehen

Published:

- with international search report
- before the expiration of the time limit for amending the  
claims and to be republished in the event of receipt of  
amendments

For two-letter codes and other abbreviations, refer to the "Guid-  
ance Notes on Codes and Abbreviations" appearing at the begin-  
ning of each regular issue of the PCT Gazette.

(54) Title: HYDANTOIN DERIVATIVES WITH AFFINITY FOR SOMATOSTATIN RECEPTORS



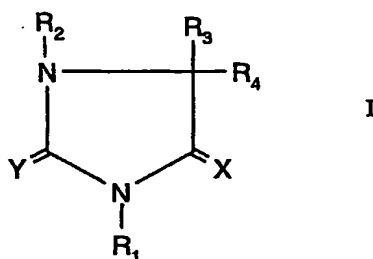
(57) Abstract: The invention provides compounds of formula (I) wherein X,  
Y, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> and R<sub>4</sub> are as defined in the description, and the preparation  
thereof. The compounds of the formula bind to somatostatin receptors and  
are useful as pharmaceuticals.

WO 01/85718 A1

## HYDANTOIN DERIVATIVES WITH AFFINITY FOR SOMATOSTATIN RECEPTORS

The present invention relates to novel hydantoin derivatives, their preparation, their use as pharmaceuticals and pharmaceutical compositions containing them.

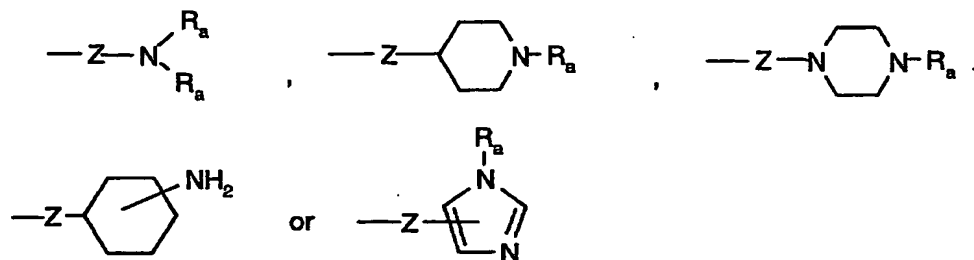
The invention provides compounds of formula I



wherein

X and Y independently are O or H, H,

R<sub>1</sub> is a group of formula

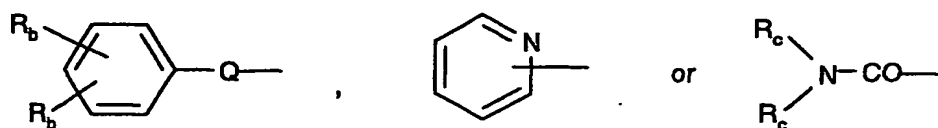


wherein the R<sub>a</sub> independently are hydrogen, C<sub>1-4</sub> alkyl or a CH<sub>3</sub>COO-CH(CH<sub>3</sub>)-OCO-group and Z is a saturated or unsaturated aliphatic C<sub>2-6</sub> hydrocarbonic chain which is (a) optionally interrupted by -O- or -S- and (b) optionally substituted by C<sub>1-4</sub> alkyl or C<sub>1-4</sub> alkoxy groups,

R<sub>2</sub> is a group of formula -SO<sub>2</sub>-Ar or -CH<sub>2</sub>-Ar wherein Ar is phenyl or naphthyl optionally mono- or di-substituted by hydroxy, halogen, C<sub>1-4</sub> alkyl, C<sub>1-4</sub>alkoxy, cyano,

- 2 -

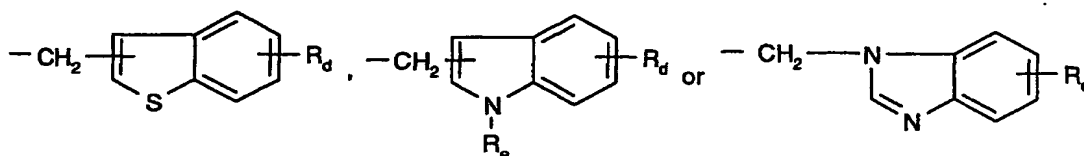
trifluoromethyl, aminomethyl, dimethylaminocarbonyl, benzimidazolyloxy or morpholinocarbonyl, or by a group of formula



wherein  $Q$  is  $CH_2$ ,  $O$ ,  $S$  or  $CO$ , the  $R_b$  independently are hydrogen,  $C_{1-4}$ alkyl,  $C_{1-4}$ alkoxy, amino, halogen, hydroxy, a  $NH_2-(CH_2)_4-CH(NH_2)-COO-$  group or form together a methylenedioxy, and the  $R_c$  independently are hydrogen or  $C_{1-4}$ alkyl,

$R_3$  is hydrogen or  $C_{1-4}$  alkyl and

$R_4$  is a group of formula



wherein  $R_d$  is hydrogen, halogen,  $C_{1-4}$  alkyl or  $C_{1-4}$ alkoxy, and  $R_e$  is hydrogen,  $C_{1-4}$ alkyl or benzyl,

in free base or acid addition salt form.

$X$  and  $Y$  are preferably  $O$ .

$R_1$  preferably is  $-Z-NH_2$ , wherein  $Z$  is preferably an alkylene chain.

$R_2$  preferably is  $-SO_2-A_r$ , wherein  $A_r$  is preferably an optionally substituted phenyl.

$R_3$  preferably is  $H$ .

- 3 -

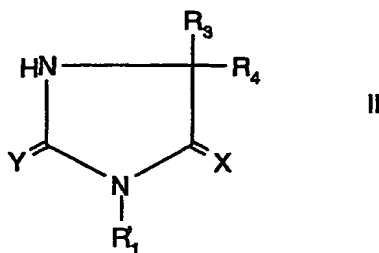
$R_4$  is preferably an optionally substituted 3-indolyl.

Any alkyl or alkoxy group as defined above preferably has one or two carbon atoms and more preferably is methyl or methoxy.

Halogen denotes fluorine, bromine or chlorine.

Depending on the nature of the substituents defined above, one or more asymmetric carbons may be present in the molecule. All optical isomers and their mixtures including the racemic mixtures are part of the present invention.

The compounds of formula I may be prepared over a process which includes the steps of reacting a compound of formula II



wherein X, Y,  $R_3$  and  $R_4$  are as defined above and  $R'_1$  is  $R_1$  as defined above or a protected form of  $R_1$ , with a compound of formula III



wherein  $R'_2$  is  $R_2$  as defined above or a protected form of  $R_2$  and Hal is chlorine, bromine or iodine, deprotecting the resulting product and recovering the thus obtained compound of formula I in free base or acid addition salt form.

A protected amino group in  $R'_1$  is for example an N-butyloxycarbonyl (Boc)- or an N<sub>3</sub>-residue. When in formula III,  $R'_2$  is a group of formula  $-\text{SO}_2\text{-A}_r$ , Hal is preferably chlorine. The condensation of the compound of formula II with the compound of

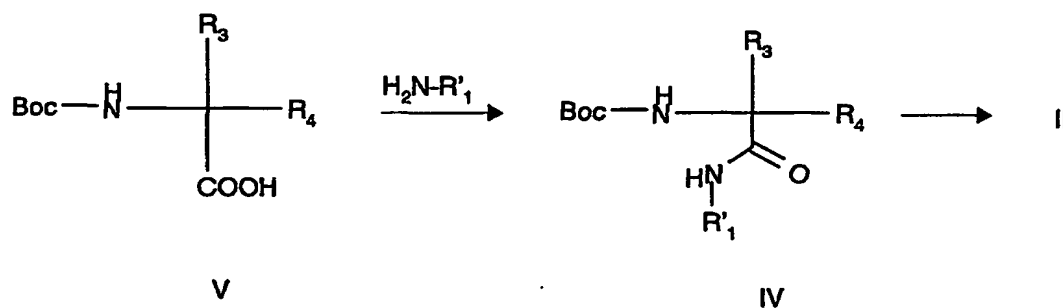
- 4 -

formula III and the subsequent deprotection can be effected according to known methods, for example as described in Example 1.

Working up the reaction mixtures obtained and purification of the compounds of formula I may also be carried out in accordance with known methods.

Acid addition salts may be produced from the free bases in known manner, and vice versa.

The starting compounds of formula II are known or may be produced by known methods. For example compounds of formula II wherein X and Y are O may be produced in accordance with the following reaction scheme, for example as described in Example 1:



The starting compounds of formulae III and V are known or may be produced by known processes.

The compounds of formula I and their physiologically acceptable acid addition salts, hereinafter referred to as compounds of the invention, have interesting pharmacological properties when tested in vitro using somatostatin receptor expressing cell cultures and in animals, and may therefore be used as pharmaceuticals.

In particular the compounds of the invention bind to somatostatin receptors. More particularly they are selective agonists at Somatostatin sst<sub>2</sub> receptors, as determined in radioligand binding and second messenger studies [see for example K. Kaupmann et al., *FEBS LETTERS* 1993, **331**: 53-59].

The compounds of the invention are therefore indicated for use in anxiety, depression, schizophrenia, neurodegenerative diseases such as dementia, epilepsy,

endocrinological disorders associated with an excess of hormone release such as: growth hormone (GH) glucagon or insulin secretion, gastro-intestinal disorders, for the treatment of tumors and for vascular disorders and immunological diseases.

The usefulness of the compounds of the invention in these indications is confirmed in a range of standard tests as indicated below:

At doses of about 0.3 to 3 mg/kg p.o., the compounds of the invention increase exploratory behavior of mice in the open half of the half enclosed platform, a model which is predictable for anxiolytic activity (Psychopharmacology, 1986, 89:31-37).

In the same half enclosed platform model, the compounds of the invention at the above indicated doses increase vigilance and exploratory components of behavior of the mice. The compounds are therefore indicated for the treatment of depression, schizophrenia and dementia, in particular of senile dementia of the Alzheimer type (SDAT). In addition, there is circumstantial clinical evidence for various types of dementias to be associated with reduced somatostatin levels [see for example J. Epelbaum et al., Clinical Reviews in Neurobiology 8: 25-44 (1994)].

At doses of about 0.3 to 3 mg/kg p.o., the compounds of the invention inhibit epileptic seizure in electrically and chemically induced episodes in rats [A. Vezzani et al., Neuropharmacol., 30: 345-352 (1991)].

Furthermore the compounds of the invention inhibit GH release in cultured pituitary cells in vitro and depress serum GH and insulin levels in the rat. The test is carried out using male rats. The test substance is administered at varying, logarithmically staggered doses employing at least 5 rats per dose. 1 hour after s.c. administration of the test substance blood is taken. The determination of the blood serum GH and insulin levels is measured by radio-immunoassay. The compounds of the invention are active in this test when administered at a dosage in the range of from 0.1 to 1 mg/kg s.c..

The inhibitory effect of the compounds on GH release may also be examined after oral application to male rats with oestradiol implants. This test is carried out as follows:

A loop (length 50 mm Ø 3 mm) of silastic with 50 mg of oestradiol is implanted under the dorsal skin of anaesthetized male OFA rats which have a weight of ca. 300 g. At various times (1 to 6 months later), these animals, in a fasted state, are used repeatedly for tests. The test substances are active in this test at doses from 0.1 to 5 mg/kg, when GH level in the blood serum is determined by radio-immunoassay 1 and 2 hours after oral administration.

The compounds of the invention are accordingly indicated for use in the treatment of disorders with an aetiology comprising or associated with excess GH-secretion, e.g. in the treatment of acromegaly as well as in the treatment of diabetes mellitus, especially complications thereof, e.g. angiopathy and various disorders associated with angiogenesis, proliferative retinopathy, dawn phenomenon and nephropathy.

The compounds of the invention also inhibit gastric and exocrine and endocrine pancreatic secretion and the release of various peptides of the gastrointestinal tract, as indicated in standard tests using e.g. rats with gastric or pancreatic fistulae.

The compounds are thus additionally indicated for use in the treatment of gastrointestinal disorders, for example in the treatment of peptic ulcers, disturbances of GI motility, enterocutaneous and pancreaticocutaneous fistula, irritable bowel syndrome, dumping syndrome, watery diarrhea syndrome, acute pancreatitis and gastro-intestinal hormone secreting tumors (e.g. vipomas, glucagonomas, insulinomas, carcinoids and the like) as well as gastro-intestinal bleeding. [see for example: Th. O'Dorisio et al., *Advances Endocrinol. Metab.* 1990, 1: 175-230].

The compounds of the invention are also effective in the treatment of various kinds of tumors, particularly of sst<sub>2</sub> receptor bearing tumors, as indicated in proliferation tests with various different cancer cell lines and in tumor growth experiments in nude mice with hormone dependent tumors [see for example: G. Weckbecker et al., *Cancer Research* 1994, 54: 6334-6337]. Thus the compounds can be used in the treatment of, for example, cancers of the breast, the prostate, the colon, the pancreas, the brain and the lung (small cell lung cancer).

- 7 -

For the above-mentioned indications, the appropriate dosage will of course vary depending upon, for example, the compound employed, the host, the mode of administration and the nature and severity of the condition being treated. However, in general, satisfactory results in animals are indicated to be obtained at a daily dosage of from 0.1 to about 50, preferably from about 0.5 to about 20 mg/kg animal body weight. In larger mammals, for example humans, an indicated daily dosage is in the range from about 1 to about 100, preferably from about 5 to about 50 mg of an agent of the invention conveniently administered, for example, in divided doses up to four times a day or in sustained release form.

The compounds of the invention may be administered in free form or in pharmaceutically acceptable salt form or complexes. Such salts and complexes may be prepared in conventional manner and exhibit the same order of activity as the free compounds.

The present invention also provides a pharmaceutical composition comprising a compound of the invention in free base form or in pharmaceutically acceptable acid addition salt form in association with a pharmaceutically acceptable diluent or carrier. Such compositions may be formulated in conventional manner. The compounds may be administered by any conventional route, for example parenterally e.g. in form of injectable solutions or suspensions, enterally, preferably orally, e.g. in the form of tablets or capsules or in a nasal or a suppository form.

Moreover the present invention provides the use of the compounds of the invention for the manufacture of a medicament for the treatment of any condition mentioned above.

In still a further aspect the invention provides a method for the treatment of any condition mentioned above, in a subject in need of such treatment, which comprises administering to such subject a therapeutically effective amount of a compound of the invention.

The following examples illustrate the invention. The temperatures are given in degrees Celsius and are uncorrected.



**Example 1: (+/-)-1-(2',5'-dichloro-1'-benzenesulfonyl)-3-(5'-amino-n-pentanyl)-5-[(indol-3-yl)-methyl]-imidazolidine-2,4-dione**

Sodium hexamethyldisilazide (1.1 mmol, 1.1mL 1M solution in THF) is added to a stirred solution of 3-[5'-amino-(N-t-butyloxycarbonyl)-n-pentanyl]-5-[(indol-3-yl)methyl]-imidazolidine-2,4-dione (415mg, 1.0mmol) in 5mL dry tetrahydrofuran (THF) at -40° under argon. After 30 minutes, 2,5-dichlorobenzenesulfonyl chloride (270mg, 1.1mmol) is added and the solution is allowed to stir overnight at room temperature. Saturated ammonium chloride solution is added and the mixture concentrated on a rotary evaporator. The mixture is then dissolved in ethyl acetate, extracted with brine, dried (sodium sulfate) and concentrated to a viscous oil. This crude product is purified by medium pressure liquid chromatography (MPLC) over silica gel (59g SiO<sub>2</sub> 0.015-0.04mm; ethylacetate-hexane 2:1) to give a colorless viscous oil.

The so obtained product (530mg, 0.85mmol) is dissolved in 6mL of dichloromethane and iodotrimethylsilane (204mg, 2.0mmol) is added. After stirring for 10 minutes at room temperature, potassium bicarbonate (4mL, 2N solution) is added and the resulting solution stirred for 15 minutes. The organic phase is separated, dried (sodium sulfate) and concentrated to give the crude free base. This base is dissolved in 4mL ethanol and ethereal HCl solution (1mL, ca. 1N solution) is added. The solution is cooled and ether added whereupon the hydrochloride salt crystallizes out of solution. Filtration provides the product in hydrochloride salt form; mp. 157-159°.

The starting imidazolidine-dione is prepared as follows:

**a) N- $\alpha$ -t-butyloxycarbonyl-d,L-tryptophan-[5-amino-(N-t-butyloxycarbonyl)-n-pentanyl] amide**

To a stirred solution of mono-N-Boc-1,5-pentanediamine (1.27g, 6.3mmol) and d,L-tryptophan (2.12g, 7.0mmol) in 30mL THF is added dicyclohexylcarbodiimide (DCC) (1.54g, 7.5mmol) at room temperature. After one hour the mixture is filtered to remove the precipitated dicyclohexylurea and concentrated in vacuo. Ether is added, the mixture is filtered and then cooled, whereupon the product crystallizes out of solution. Filtration yields the product as a light brown powder; mp. 97-98°.

**b) 3-[5'-amino-(N-t-butyloxycarbonyl)-n-pentanyl]-5-[(indol-3-yl)-methyl]-imidazolidine  
2,4-dione**

The product obtained under a) (2.93g, 6.0mmol) is dissolved in 50mL THF and heated under reflux with tetrabutylammonium fluoride trihydrate (5.68g, 18mmol). After 24 hours the mixture is concentrated in vacuo. The residue is dissolved in ethylacetate, extracted with brine, dried (sodium sulfate) and concentrated to a viscous brown oil. MPLC chromatography (138g SiO<sub>2</sub>; ethylacetate-hexane 2:1) gives the product as a light yellow oil which crystallizes upon standing. An analytical sample is prepared by recrystallization from ethylacetate-hexane; mp. 136-137°.

The compounds of formula I wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> and R<sub>4</sub> are as defined in the following table 1 and X and Y are both O as well as the compounds of formula I wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> and R<sub>4</sub> are as defined in the following table 2, X is H, H and Y is O, are prepared in analogous manner to Example 1.

Table 1

Ex	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	R <sub>4</sub>
2	-(CH <sub>2</sub> ) <sub>5</sub> -NH <sub>2</sub>	-SO <sub>2</sub> -p-toluyI	H	-CH <sub>2</sub> -3 indolyl
3	"	-SO <sub>2</sub> -3,4-diMe-Ph	"	"
4	"	-SO <sub>2</sub> -m-CH <sub>3</sub> -Ph	"	"
5	"	-SO <sub>2</sub> -o-OMe-Ph	"	"
6	-CH <sub>2</sub> -CH=CH-(CH <sub>2</sub> ) <sub>2</sub> -NH <sub>2</sub> (cis)	-SO <sub>2</sub> -3,4-diOMe-Ph	"	"
7	-(CH <sub>2</sub> ) <sub>2</sub> -O-(CH <sub>2</sub> ) <sub>2</sub> -NH <sub>2</sub>	"	"	"
8	-(CH <sub>2</sub> ) <sub>4</sub> -NH <sub>2</sub>	"	"	"
9	-(CH <sub>2</sub> ) <sub>6</sub> -NH <sub>2</sub>	"	"	"
10	-(CH <sub>2</sub> ) <sub>5</sub> -NH <sub>2</sub>	-SO <sub>2</sub> -3-[(Me) <sub>2</sub> NCO]-4-(5-benzimidazolyl-O)-Ph	"	"
11	"	-SO <sub>2</sub> -p-(p-NH <sub>2</sub> -Ph-O)-Ph	"	"
12	"	-SO <sub>2</sub> -3-CN-4-(p-OH-Ph-O)-Ph	"	-CH <sub>2</sub> -3-(7-CH <sub>3</sub> -indolyl)
13	"	-SO <sub>2</sub> -3-NH <sub>2</sub> CH <sub>2</sub> -4-(p-OH-Ph-O)-ph	"	"
14	"	-SO <sub>2</sub> -p-(p-OH-Ph-CO)-Ph	"	-CH <sub>2</sub> -3-indolyl
15	"	-SO <sub>2</sub> -p-(p-OH-Ph-CH <sub>2</sub> )-Ph	"	"
16	"	-SO <sub>2</sub> -p-(p-OH-Ph-O)-Ph	"	"
17	"	-SO <sub>2</sub> -p-(p-OH-Ph-S)-Ph	"	"
18	"	-SO <sub>2</sub> -p-(4-NH <sub>2</sub> -2-pyridyl-O)-Ph	"	"

Ex	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	R <sub>4</sub>
19	-(CH <sub>2</sub> ) <sub>5</sub> -NH <sub>2</sub>	-SO <sub>2</sub> -3-(morpholino-CO)-4-(p-Cl-Ph-O)-Ph	H	-CH <sub>2</sub> -3-indolyl
20	4-piperidiny-(CH <sub>2</sub> ) <sub>2</sub> -	-SO <sub>2</sub> -3-[(Me) <sub>2</sub> NCO]-4-(p-OH-Ph-O)-Ph	"	"
21	-(CH <sub>2</sub> ) <sub>5</sub> -NH <sub>2</sub>	-SO <sub>2</sub> -3-[(Me) <sub>2</sub> NCO]-4-(3-Cl-4-OH-Ph-O)-Ph	"	"
22	4-Me-1-piperaziny-(CH <sub>2</sub> ) <sub>2</sub> -	-SO <sub>2</sub> -3-[(Me) <sub>2</sub> NCO]-4-(p-OMe-Ph-O)-Ph	"	"
23	-(CH <sub>2</sub> ) <sub>5</sub> -NH <sub>2</sub>	-SO <sub>2</sub> -3-[(Me) <sub>2</sub> NCO]-4-[NH <sub>2</sub> -(CH <sub>2</sub> ) <sub>4</sub> -CH(NH <sub>2</sub> )-COO-Ph-O]-Ph	"	"
24	[MeCOO-CH(Me)-OCO-NH]-(CH <sub>2</sub> ) <sub>5</sub> -	-SO <sub>2</sub> -3-[(Me) <sub>2</sub> NCO]-4-(p-OH-Ph-O)-Ph	"	"
25	-(CH <sub>2</sub> ) <sub>5</sub> -NH <sub>2</sub>	-SO <sub>2</sub> -3-[(Me) <sub>2</sub> NCO]-4-(3-Cl-4-OH-Ph-O)-Ph	"	-CH <sub>2</sub> -3-(7-Cl-inc
26	-CH <sub>2</sub> -(p-trans-NH <sub>2</sub> -cyclohexyl)	-SO <sub>2</sub> -3-[(Me) <sub>2</sub> NCO]-4-(p-OH-Ph-O)-Ph	"	-CH <sub>2</sub> -3-indolyl
27	-(CH <sub>2</sub> ) <sub>5</sub> -N(Me) <sub>2</sub>	-SO <sub>2</sub> -3-[(Me) <sub>2</sub> NCO]-4-(3-Cl-4-OH-Ph-O)-Ph	"	"
28	-(CH <sub>2</sub> ) <sub>3</sub> -(1-imidazolyl)	"	"	"
29	-(CH <sub>2</sub> ) <sub>5</sub> -NH <sub>2</sub>	-SO <sub>2</sub> -3-[(Me) <sub>2</sub> NCO]-4-(3-Cl-4-OH-Ph-O)-Ph	"	-CH <sub>2</sub> -3-(7-Me-indolyl)

Ex	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	R <sub>4</sub>
30	-(CH <sub>2</sub> ) <sub>5</sub> -NH <sub>2</sub>	-SO <sub>2</sub> -3-[(Me) <sub>2</sub> NCO]-4-(3-Cl-4-OH-Ph-O)-Ph	H	-CH <sub>2</sub> -3-(5-Me-indolyl)
31	-(CH <sub>2</sub> ) <sub>4</sub> -CH(Me) <sub>2</sub> -NH <sub>2</sub>	-SO <sub>2</sub> -3-[(Me) <sub>2</sub> NCO]-4-(3-Cl-4-OH-Ph-O)-Ph	"	-CH <sub>2</sub> -3-(7-Me-indolyl)
32	-(CH <sub>2</sub> ) <sub>3</sub> -(1-Me-4-imidazolyl)	"	"	-CH <sub>2</sub> -3-indolyl)
33	-(CH <sub>2</sub> ) <sub>5</sub> -NH <sub>2</sub>	-SO <sub>2</sub> -3-CH(CH <sub>3</sub> ) <sub>2</sub> -4-(3-Cl-4-OH-Ph-O)-Ph	"	-CH <sub>2</sub> -3-(7-Me-indolyl)
34	-(CH <sub>2</sub> ) <sub>4</sub> -C(CH <sub>3</sub> ) <sub>2</sub> -NH <sub>2</sub>	-SO <sub>2</sub> -3-[(Me) <sub>2</sub> NCO]-4-(p-F-Ph-O)-Ph	"	"
35	"	-CH <sub>2</sub> -3-[(Me) <sub>2</sub> NCO]-4-(3-Cl-4-MeO-Ph-O)-Ph	"	"
36	"	-SO <sub>2</sub> -3-[(Me) <sub>2</sub> NCO]-4-(3,4-diCl-Ph-O)-Ph	"	"
37	"	-SO <sub>2</sub> -3-[(Me) <sub>2</sub> NCO]-4-(3-Cl-4-OH-Ph-O)-Ph	"	-CH <sub>2</sub> -3-benzo[b]thienyl
38	"	-SO <sub>2</sub> -3-[(Me) <sub>2</sub> NCO]-4-(3-Cl-4-MeO-Ph-O)-Ph	"	-CH <sub>2</sub> -1-(4-Me-benzimidazolyl)
39	-(CH <sub>2</sub> ) <sub>4</sub> -C(CH <sub>3</sub> ) <sub>2</sub> -NH <sub>2</sub>	-SO <sub>2</sub> -3-[(Me) <sub>2</sub> NCO]-4-[(3,4-methylenedioxy-Ph-O)-Ph	"	-CH <sub>2</sub> -3-(7-Me-indolyl)

Me = methyl; Ph = phenyl

Table 2

Ex	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	R <sub>4</sub>
40	-CH <sub>2</sub> -CH=CH-(CH <sub>2</sub> ) <sub>2</sub> -NH <sub>2</sub>	-CH <sub>2</sub> -Ph	H	-CH <sub>2</sub> -3-indolinyI
41	"	"	"	-CH <sub>2</sub> -3-indolyl
42	-(CH <sub>2</sub> ) <sub>5</sub> -NH <sub>2</sub>	"	"	"
43	-CH <sub>2</sub> -p-(aminomethyl)-Ph	"	"	"
44	-(CH <sub>2</sub> ) <sub>5</sub> -NH <sub>2</sub>	-SO <sub>2</sub> -3,4-dioMe-Ph	"	"
45	"	-SO <sub>2</sub> -p-(p-OH-Ph-O)-Ph	"	"

Me = methyl; Ph = phenyl

The compounds of the above tables have been characterized as follows:

- Example 2 FAB-MS:  $MH^+ = 469$
- 3 FAB-MS:  $MH^+ = 515$
- 4 FAB-MS:  $MH^+ = 523$
- 8 FAB-MS:  $MH^+ = 515$
- 9 FAB-MS:  $MH^+ = 529$
- 
- 12 FAB-MS:  $MH^+ = 602$   
NMR (DMSO): 0.4 - 1.1 (6H,m), 2.3 (2H,t), 2.4 (3H,s), 2.9 (1H,m), 3.05 (1H,m), 3.2 - 2.6 (2H,s), 3.5 (2H,d), 5.2 (1H,t), 6.8 - 7.1 (9H,m), 7.3 (1H,m), 8.2 (1H,m), 8.55 (1Hm), 11.0 (1H,s).
- 
- 13 FAB-MS:  $MH^+ = 606$   
NMR (DMSO): 0.4 - 1.6 (6H,m), 2.4 (3H,t), 2.5 (2H,m), 2.9 (1H,m), 3.1 (1H,m), 3.5 (2H,m), 4.2 (2H,m), 5.25 (1H,m), 6.7 - 7.1 (8H,m), 7.35 (1H,m), 7.9 (1H,m), 8.05 (3H,s), 8.3 (1H,m), 8.75 (3H,s), 9.75 (1H,s), 11.1 (1H,s).
- 
- 14 Mp: 151-153° (HCl salt)  
FAB-MS:  $MH^+ = 575$   
NMR (DMSO): 0.45 - 1.1 (6H,m), 2.25 (2H,m), 2.9 (1H,m), 3.05 (1H,m), 3.2 (2H,s), 3.65 (1H,m), 3.7 (1H,q), 3.85 (3H,s), 5.2 (1H,t), 6.9 - 8.2 (13H,m), 11.0 (1H,s).
- 
- 15 FAB-MS:  $MH^+ = 561$   
NMR (DMSO): 0.4 - 1.0 (6H,m), 2.25 (2H,m), 2.85 (1H,m), 3.05 (1H,m), 3.2 (2H,s), 3.5 (2H,d), 3.7 (3H,s), 4.0 (2H,s), 5.1 (1H,t), 6.8 - 8.0 (13H,m), 11.0 (1H,s).
- 
- 16 FAB-MS:  $MH^+ = 563$
- 
- 17 FAB-MS:  $MH^+ = 579$

- 15 -

- 19 FAB-MS:  $MH^+ = 694$
- 20 FAB-MS:  $MH^+ = 660$
- 21 FAB-MS:  $MH^+ = 668$   
NMR (Hcl salt; DMSO): 0.35 - 1.2 (6H,m), 2.45 (2H,m), 2.85 (3H,s), 3.0 (3H,s),  
2.85 - 3.15 (2H,m), 3.5 (2H,d), 5.65 (1H,t), 6.9 - 7.1 (6H,r  
7.2 (1H,d), 7.35 (1H,d), 7.5 (1H,d), 7.75 (3H,s), 8.0 (2H,m  
10.4 (1H,s), 11.1 (1H,s).
- 22 ESI-MS:  $M^+ = 689$
- 23 Mp: 189-191° (amorphous)
- 24 Mp: 107-111° (amorphous)
- 25 Mp: 198-203°
- 26 Mp: 190-196° (amorphous)
- 27 ESI-MS:  $M^+ = 696$
- 28 ESI-MS:  $M^+ = 691$
- 29 FAB-MS:  $MH^+ = 682$
- 30 FAB-MS:  $MH^+ = 682$
- 31 FAB-MS:  $MH^+ = 710$   
NMR (DMSO): 0.45 - 1.1 (6H,m), 0.9 (6H,2s), 2.4 (3H,s), 2.85 (3H,s), 3.0  
(3H,s), 2.8 - 3.1 (2H,m), 3.5 (2H,d), 5.65 (1H,t), 6.8 - 7.05  
(6H,m), 7.2 (1H,d), 7.3 (1H,d), 8.0 (2H,m), 11.0 (1H,s).



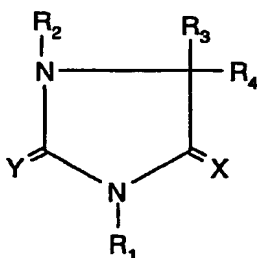
- 16 -

- 32 ESI-MS:  $M^+ = 705$   
NMR (DMSO): 1.1 (2H,m), 1.8 (2H,t), 2.8 (3H,s), 2.95 (3H,s), 3.05 (2H,m),  
3.5 (2H,d), 3.55 (3H,s), 5.6 (1H,t), 6.45 (1H,s), 6.85 - 7.05  
(5H,m), 7.2 - 7.5 (4H,m), 8.0 (2H,m), 10.3 (1H,s), 10.95  
(1H,s)
- 33 ESI-MS:  $M^+ = 653$
- 34 ESI-MS:  $M^+ = 678$
- 35 FAB-MS:  $MH^+ = 674$   
NMR (DMSO): 0.9 (6H,s), 0.8 - 1.4 (6H,m), 2.4 (3H,s), 2.8 (3H,s), 2.95  
(3H,s), 3.0 - 3.5 (4H,m), 3.85 (3H,s), 4.2 (1H,t), 4.35 (1H,d),  
4.8 (1H,d), 6.8 - 7.35 (10H,m), 10.9 (1Hs).
- 36 FAB-MS:  $MH^+ = 728$
- 37 FAB-MS:  $MH^+ = 685$
- 38 FAB-MS:  $MH^+ = 697$
- 39 ESI-MS:  $M^+ = 704$

- 17 -

## WHAT WE CLAIM IS:

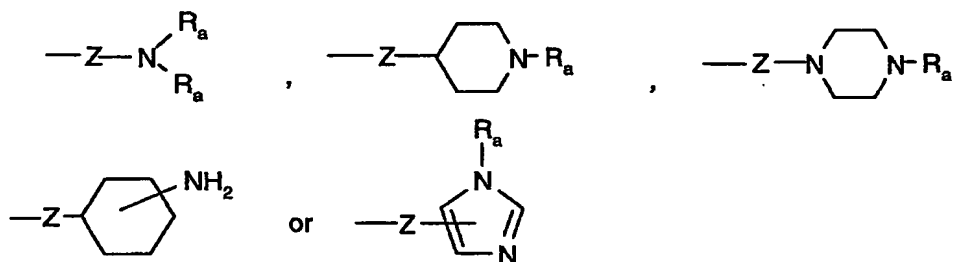
1. A compounds of formula I



wherein

X and Y independently are O or H, H,

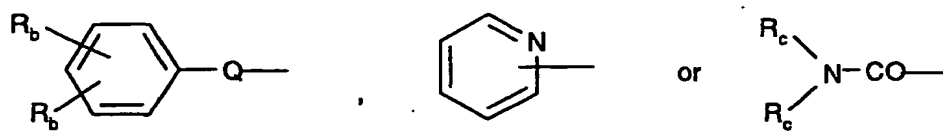
R<sub>1</sub> is a group of formula



wherein the R<sub>a</sub> independently are hydrogen, C<sub>1-4</sub> alkyl or a CH<sub>3</sub>COO-CH(CH<sub>3</sub>)-OCO-group and Z is a saturated or unsaturated aliphatic C<sub>2-6</sub> hydrocarbonic chain which is (a) optionally interrupted by -O- or -S- and (b) optionally substituted by C<sub>1-4</sub> alkyl or C<sub>1-4</sub> alkoxy groups,

R<sub>2</sub> is a group of formula -SO<sub>2</sub>-Ar or -CH<sub>2</sub>-Ar wherein Ar is phenyl or naphthyl optionally mono- or di- substituted by hydroxy, halogen, C<sub>1-4</sub> alkyl, C<sub>1-4</sub>alkoxy, cyano, trifluoromethyl, aminomethyl, dimethylaminocarbonyl, benzimidazolylloxy or morpholinocarbonyl, or by a group of formula

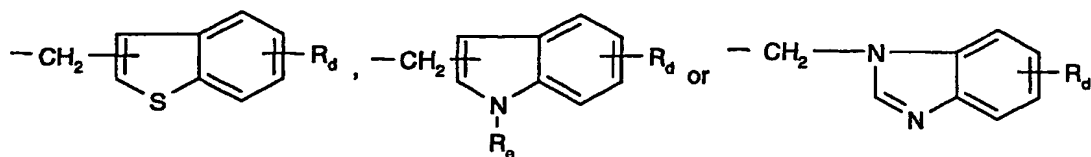
- 18 -



wherein  $Q$  is  $CH_2$ ,  $O$ ,  $S$  or  $CO$ , the  $R_b$  independently are hydrogen,  $C_{1-4}$ alkyl,  $C_{1-4}$ alkoxy, amino, halogen, hydroxy, a  $NH_2-(CH_2)_4-CH(NH_2)-COO-$  group or form together a methylenedioxy, and the  $R_c$  independently are hydrogen or  $C_{1-4}$ alkyl,

$R_3$  is hydrogen or  $C_{1-4}$  alkyl and

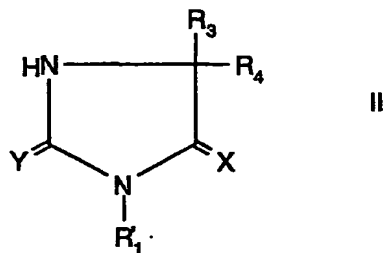
$R_4$  is a group of formula



wherein  $R_d$  is hydrogen, halogen,  $C_{1-4}$  alkyl or  $C_{1-4}$ alkoxy, and  $R_6$  is hydrogen,  $C_{1-4}$ alkyl or benzyl,

in free base or acid addition salt form.

2. A process for the preparation of a compound of formula I as defined in claim 1, which includes the steps of reacting a compound of formula II



- 19 -

wherein X, Y, R<sub>3</sub> and R<sub>4</sub> are as defined in claim 1 and R'<sub>1</sub> is R<sub>1</sub> as defined in claim 1 or a protected form of R<sub>1</sub>, with a compound of formula III



wherein R'<sub>2</sub> is R<sub>2</sub> as defined in claim 1 or a protected form of R<sub>2</sub> and Hal is chlorine, bromine or iodine, deprotecting the resulting product and recovering the thus obtained compound of formula I in free base or acid addition salt form.

3. A pharmaceutical composition comprising a compound of formula I as defined in claim 1 in free base form or in pharmaceutically acceptable acid addition salt form in association with a pharmaceutically acceptable carrier or diluent.

4. A compound of formula I as defined in claim 1 in free base form or in pharmaceutically acceptable acid addition salt form, for use as a pharmaceutical.

5. A compound of claim 1 in free base or pharmaceutically acceptable acid addition salt form, for use in the treatment of conditions responsive to sst<sub>2</sub> receptor agonists.

6. The use of a compound of claim 1 in free base or pharmaceutically acceptable acid addition salt form, as a pharmaceutical for the treatment of conditions responsive to sst<sub>2</sub> receptor agonists.

7. The use of a compound of claim 1 in free base or pharmaceutically acceptable acid addition salt form, for the manufacture of a medicament for the treatment of conditions responsive to sst<sub>2</sub> receptor agonists.

8. A method for the treatment of conditions responsive to sst<sub>2</sub> receptor agonists to a subject in need of such treatment, which comprises administering to such subject a therapeutically effective amount of a compound of claim 1 in free base or pharmaceutically acceptable acid addition salt form.

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 01/05162

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D403/06 C07D403/14 C07D401/14 C07D409/06 A61K31/4166  
A61P25/00

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,A	WO 01 09090 A (THURIEAU CHRISTOPHE ;POITOUT LYDIE (FR); BRAULT VALERIE (FR); SOD) 8 February 2001 (2001-02-08) claim 1	1-8
A	SCICINSKI J J ET AL: "The solid phase synthesis of a series of tri-substituted hydantoin ligands for the somatostatin SST5 receptor" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, GB, OXFORD, vol. 8, no. 24, 15 December 1998 (1998-12-15), pages 3609-3614, XP004150376 ISSN: 0960-894X * Compounds 11-20 *	1-8

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

## \* Special categories of cited documents:

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

\*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

\*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

\*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

\*G\* document member of the same patent family

Date of the actual completion of the international search

25 July 2001

Date of mailing of the international search report

17/09/2001

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Johnson, C

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 01/05162

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0109090 A	08-02-2001	FR 2796945 A AU 7009100 A	02-02-2001 19-02-2001